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Improvement of Galton–Watson Branching Process (GWBP) for Mathematical Optimization of Cancer Treatment

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Abstract

Biologists have uncovered some of the most basic mechanisms by which normal cells develop into cancerous tumors. These biological theories can be transformed into adequate mathematical models. For this reason, we attempt to study the evolution of cancer cells using the GWBP. The purpose of this paper is to study how the genetic algorithm (GA) can be used to follow the evolution of cancer and find optimal chemotherapeutic treatments.The development of GWBP give us the evolution of number of cancer cells for any patient if the death rate will defined experimentally, according to this value we can simulate the suitable chemotherapy treatments which cause the death of cancer, then determine the minimum dosage treatment injected using the GA optimization method. Analysis of these results gives us the objective function, who gives us a minimum in terms of number of cancer cells, with maximum in terms of cumulative treatment dosage.

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1. Introduction

Cancer is one of the major diseases that limited the human life; it is treated with surgery, radiation, chemotherapy, hormones, and immunotherapy. The development in cancer prevention, detection, treatment, and management is recently very advanced. Recently, many mathematical models of cancer mechanisms have

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been developed to aid in the understanding of the biological processes of cancer. The interest in developing such models is their ability to regroup a large amount of information accumulated by biologists and, therefore, to find ways to follow the evolution of this disease and optimize suitable treatments.

The concept of applying optimal control to different disease states starts by the mid of 70s and since then, it is the subject of various publications. In [1] engineering optimal control theory is applied to investigate on the drug regimen for reducing an experimental tumor cell population. Swan [1] presents a study that has used engineering optimal control theory for a chemotherapy problem. It involves a human tumor and minimizes the total amount of used drug for a specified value of tumor cell population. The first published review of optimal control problems in the general area of cancer research appeared in [2]. In later papers, for example [3] and [4], Swan provides evidence for the use of continuous delivery of drugs. An excellent general reference for this whole topic is [5]. But in [6], Zietz and Nicolini attempted a compromise between toxicity and cell kill by using an objective function that is a combination of tumor cell final and normal population. As a different methodology, like in [7] and [8], the application of drugs is matched up with the progression of the cells through the cell cycle. In [6] the optimal period for drug application corresponds approximately to the normal cell cycle time. Most of these references concern treatment of solid tumors or cancer treatment in general.

Before reaching the optimization step we need to study the modelling of cancer cells. For this reason, we are interested to study models that describe the evolution of cancer cells, assembly the protocols of cancer treatment; to achieve the optimal problem allows us to give each patient the optimal treatment, while killing the largest number of cancer cells.

In fact, observations in biological cases are often presented in a fuzzy way. For this reason, we attempt to introduce probabilities, which are used in stochastic models. Among the various stochastic models that are able to describe biological processes, such as cancer, we have the following: Moran Model [20], Wright-Fisher (WF) Model [9, 10, 11], Galton–Watson branching process (GWBP) [12, 13], Markov chain Processes [14], and Model of Moolgavkar, Venzon, and Knudson (MVK) [15].

However, in our studies real case of cancer were modelled according to the GWBP methodologies, simulated and optimized according to GA strategy. The GWBP model is a stochastic model that defines the pattern of population growth using sums of identical and independent (iid) random variables; the population evolves from generation to generation, with the individuals receiving iid numbers of children [12]. This model introduces the case of cancer in [13], but it was not applied to a real case and don't study the influence of treatment in the number of cancer cells.

In this paper, we apply chemotherapy protocols on the GWBP model that deal with cancer cells evolution and determine their simulations and optimization according to different objective functions. The section II of this paper presents the description and the characteristics of the GWBP models used in this study and the new points added so that we can use this model in the optimization of real case of cancer.

Section III presents the case study of the real case for the colon cancer using GWBP model and its optimization. Finally, section IV presents the discussion, of the simulated model according to the new point added, and of the optimized model according to different objective functions.

2. The Galton-Watson Branching Process

2.1. Description

The Galton–Watson process is the oldest, simplest and best-known branching process, which can be described as follows [16].

A single ancestor particle lives for exactly one unit of time, and at the moment of death, it produces a random number of progeny according to a prescribed probability distribution. Each of the first-generation progeny behaves as the initial particle did, independently of one another. Each particle lives for a unit of time

and produces a random number of progeny. Each of the second-generation progeny behaves in an identical way, and so forth. We will consider X to be a random variable with values in N that describe the number of children of one individual, i.e., the probability for i children is given by $P(X = i)$. Let p_i be defined by $P(X = i) = p_i$. Now, Z_n is the population size in generation n, i.e., an N-valued random variable. Furthermore, let $X_1 ... X_{Z_n}$ be i.i.d. random variables, distributed similar to X (the number of offspring of one individual). Then,

$$Z_{n+1} = \sum^{Z_n} X_i \tag{1}$$

will be the population in generation n+1, which consists of the offspring of a generation. This process is called a branching process and, more specifically, a Galton-Watson process (a general branching process may also live in continuous time) [21]. We assume that driver mutations reduce the probability that the cell will take this second course, i.e., that it will differentiate, die, or senesce (henceforth grouped as "stagnate").

Therefore, a cell with k driver mutations has a death probability and division probability as, respectively [6]:

$$d = (1-s)^k \qquad and \qquad b = 1-d \tag{2}$$

The parameter s characterizes the selective advantage provided by a driver mutation, in (2) the influence of the treatment does not appear, based on this equation, we account for the effect of the drug on the growth of cells. Because the cells are characterized by their selective coefficient, then s will increase with the drug probability and vice versa $(0 \le s \le 1)$. Thus, we will have:

$$0 \le s \le 0.5 \quad if \ q \le 0.5 \qquad or \qquad 0.5 \le s \le 1 \quad if \ q \ge 0.5$$

and q is the probability of providing u_0 dose in chemotherapy treatment [14].

$$q = 1 - e^{-\alpha u} \tag{3}$$

According to (2) and (3), the influence of treatment in the GWBP is appearing as follow:

$$d = (1 - q \times s)^k \qquad and \qquad b = 1 - d \tag{4}$$

An important parameter in determining how the sequence $\{Z_n\}_{n \ge 0}$ behaves for large n is the offspring mean [5]:

$$m = \sum_{j=1}^{\infty} j p_j \tag{5}$$

Where P_j is the probability of the death or birth of a cell and j varies from 1 to the number of cancer cells available in the generation. This mean has been discussed in detail in [17].

2.2. Characteristics

This model works far away from the target theory and studies the transformation that occurs when the first cell (among many at risk within a definite cancer type) accumulates a set of driver mutations [18]. The driver mutations are the mutations that cause cancer cells to grow. The analysis of this model yields a simple algebraic equation, which requires the initial number of cancer cells, the death and birth rates of cells, the number of driver mutations, and the selective advantage [18]. According to [17], we studied the equations for the calculation of cancer cells. However, these equations do not take into consideration the treatment effect on the cells. In this paper, we have collected these equations and related the dose effect to the selective advantage. Additionally, we calculated the death and birth rates according to (2), and we have applied them to a real cancer type, colon cancer. We studied the cell simulations according to real chemotherapy treatment protocols.

3. Case Study

Colon cancer will be used as the real case for the Branching Galton-Watson model because the parameters that represent this cancer are compatible with the parameters that describe the model. This case is characterized by the following parameters [19]:

- Cancer cells divide once every four days.
- Colon cancer requires 5 driver mutations to appear in the human body (k = 5).
- Initial number of cancer cells, $C_0 = 6*10^8$ or 12*10 cells.
- Total amount of drug is u = 3200 mg/m^2 [18].

The protocol treatment will be as follows:

Simplified LV5FU2: Folinic acid 400 mg/m^2 for 2 h placed in 250 ml G 5 %; then, 5 FU 400 mg/m^2 for 10 min placed in 100 ml de G 5 %; and then, 5 FU 2400 mg/m^2 in continuous perfusion for 46 h placed in G 5 %. This protocol is repeated every 14 days for a period of 2 months [18].

3.1. Simulations

Using MATLAB code, we determine the simulation curve of treatment protocol (Fig. 1), whose describe the number of cancer cells (c) in three cases (patient died (Fig. 4), patient cured (Fig. 3), and patient in stable case (Fig. 2) who need to repeat the protocol treatment after some time). In this model, the parameter that affects the result of the simulation is the death rate (d).

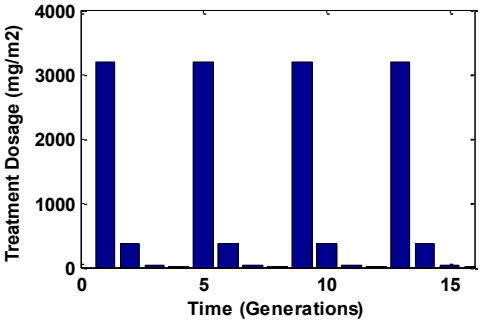

Fig. 1 Treatment protocol of colon cancer

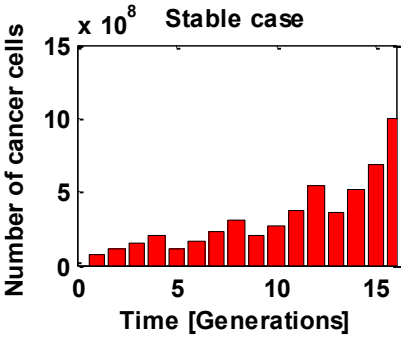

Fig. 2 Evolution of cancer in stable case

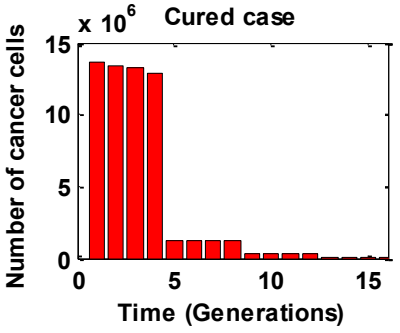

Fig.3 Evolution of cancer in cured case

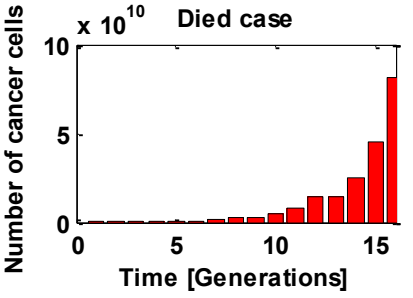

Fig. 4 Evolution of cancer in died case

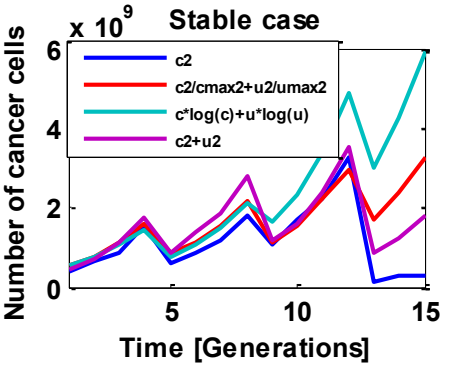

Fig. 5 Evolution of cancer cells after optimization

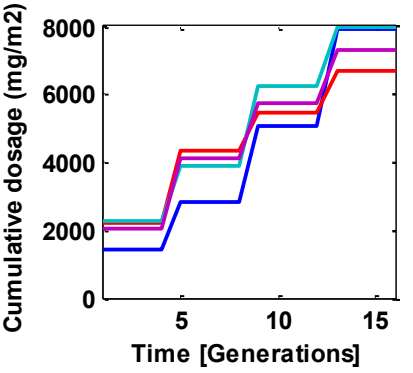

Fig. 6 Cumulative treatment dosages after optimization

3.2. Optimizations

Now, using the GA, we show the result of the optimized protocol cited above, represented in Fig. 6, using five objectives functions according to (6) to show the best minimizing of cancer cells represented in Fig.5, for a patient in stable case.

$$\int_{T_i}^{T_f} c^2 dt, \quad \int_{T_i}^{T_f} (c^2+u^2)dt, \quad \int_{T_i}^{T_f} (c\times\log(c)+u^2)dt, \quad \int_{T_i}^{T_f} (c\log c+u\log u)dt \tag{6}$$

$$\text{and} \quad \int_{T_i}^{T_f} \left(\frac{c^2}{c_{\max}^2}+\frac{u^2}{u_{\max}^2}\right)dt,$$

$$\begin{cases} c_{\max}: \text{maximum number of cancer cells} \\ u_{\max}: \text{maximum dosage treatment} \end{cases}$$

4. Discussion

Fig. 1 show the protocol treatment applied for the colon cancer, in this protocol we inject the drug with maximum dosage every 5 generations (20 days), the evolution of cancer cells varies according to the patient

case. In Fig. 2, we show the number of cancer cells for a patient in stable case, in this case d = 0.3 without treatment and d = 0.7 with treatment, starting with $C_0 = 8*10^7$ cells, this number increase slowly throughout the treatment period, but in Fig.3 this number decrease during the treatment period because the patient have a higher death rate (d = 0.9) with treatment and d = 0.4 without treatment, finally, in Fig.4 the patient die after the number of cancer cells reach 10^{12} cells, this patient have a lower death rate (d = 0.1) without treatment and d = 0.5 with treatment, for this reason the cancer growing rapidly. In general, the death rate is less than 0.5 without treatment, between 0.5 and 1 with treatment. In our cases the value of d is chosen by hazard to cover all the possibility.

Without optimization the patients in three cases, cure, death or stable, receive a total amount of dosage of 12800 mg/m^2 during the treatment period. Appling the GA in our simulated model for a patient in stable case, using five objectives functions, give us the cumulative treatment through the period treatment in Fig. 5 and the number of cancer cells according this treatment dosage in Fig. 6. Analysis of this results show that the objective function $J = \int_0^{T_f} C^2 dt$, give us a minimum in terms of number of cancer cells, with maximum in terms of cumulative treatment dosage (7920 mg/m^2) compared with other objectives functions, but this value is minimum according to the cumulative dosage without optimization.

The GWBP give us the evolution of number of cancer cells for any patient if the death rate will defined experimentally, according to this value we can determine the minimum dosage treatment injected using the GA optimization method.

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